

REMARKS

Reconsideration of the present application is respectfully requested in view of the above amendments and the following remarks. Claims 27-52 are pending and currently under examination in the application. Without acquiescence to the rejections, claims 27-28, 32-34, 38-40, 44-46, and 50-51 are amended and new claims 53-56 are added to more particularly point out and distinctly claim certain embodiments of Applicant's invention. No new matter has been added by the amendments. Support for the amendments can be found throughout the specification as filed, for example, at page 8, line 25; page 80, lines 2-5; and page 82, lines 10-13.

Rejections Under 35 U.S.C. § 112, First Paragraph, Written Description (New Matter)

The Examiner rejected claims 27-52 under 35 U.S.C. § 112, first paragraph, for allegedly containing new matter. The Examiner asserts that the original application does not envision either including or excluding polynucleic acid based cytotoxic agents.

Applicant traverses this rejection and submits that the instant claims satisfy the written description requirement. Nonetheless, without acquiescence to the rejection, the instant claims as presently amended recite "chemotherapeutic agent," support for which can be found throughout the specification, for example, at page 82, lines 10-13. This amendment obviates the Examiner's objection. Applicant further submits that the art-recognized meaning of "chemotherapeutic agent" cannot be reasonably construed to include nucleic acid based agents, such as those associated with gene therapy protocols.

Applicant submits that the instant claims satisfy the written description requirement under 35 U.S.C. § 112, first paragraph, and respectfully request withdrawal of this rejection.

Rejections Under 35 U.S.C. § 112, Second Paragraph, Indefiniteness

The Examiner rejected claims 27-38 under 35 U.S.C § 112, second paragraph, for alleged indefiniteness. The Examiner asserts that the recitation “the efficacy” lacks antecedent basis.

Applicant traverses this rejection and submits that the instant claims are clear. In particular, the failure to provide explicit antecedent basis for terms does not always render a claim indefinite; if the scope of a claim would be reasonably ascertainable by those skilled in the art, then the claim is not indefinite. *See, e.g.,* M.P.E.P. § 2173.05(e), citing *Energizer Holdings Inc. v. Int'l Trade Comm'n*, 435 F.3d 1366 (Fed. Cir. 2006). Here, despite the alleged lack of antecedent basis for the recitation “the efficacy,” the scope of “a method for enhancing *the efficacy* of a chemotherapeutic agent for a cancer cell” is reasonably ascertainable to a person skilled in the art.

Nonetheless, without acquiescence to the rejection, claims 27 and 33 recite “a method for enhancing *efficacy* of a chemotherapeutic agent for a cancer cell,” rendering moot this rejection by the Examiner. Accordingly, Applicant submits that the instant claims satisfy the requirements of definiteness under 35 U.S.C. § 112, second paragraph, and request withdrawal of this rejection.

Rejection Under 35 U.S.C. § 102, Alternatively § 103

The Examiner rejected claims 27-28, 32-34, 38-40, 44-46, and 50 under 35 U.S.C. § 102(e) for alleged lack of novelty, or, in the alternative, under 35 U.S.C. § 103(a) for alleged obviousness over Falk *et al.* (U.S. Patent No. 5,985,850). The Examiner asserts that Falk *et al.* teach the use of hyaluronan within the claimed molecular weight range of 400,000 and 900,000 Da in combination with an anti-neoplastic agent, and further asserts that the method of Falk *et al.* would inherently enhance the efficacy of the agent for a cancer cell.

Applicant traverses these rejections and submits that the instant claims are both novel and non-obvious over Falk *et al.* Embodiments of the present invention relate, in pertinent part, to method for enhancing efficacy of a chemotherapeutic agent for a cancer cell, said method comprising administering to a subject hyaluronan and the chemotherapeutic agent, wherein the hyaluronan has a molecular weight between 400,000 and 900,000 Da.

With regard to the rejection under section 102(e), Applicant submits that Falk *et al.* fail to teach, either explicitly or inherently, each feature of the instant claims. As previously made of record, Falk *et al.* fail to teach or suggest that the efficacy of a chemotherapeutic agent may be enhanced by administering a composition containing hyaluronan and the agent, and further fail to disclose with *sufficient specificity* a composition having the presently claimed molecular weight range of hyaluronan.

Contrary to the Examiner's discussion at page 6 of the Action, Falk *et al.* do not disclose, inherently or explicitly, that the hyaluronic acid (HA) based compositions provided therein may be utilized to enhance the efficiency of a chemotherapeutic agent. Rather, to rely on an inherency theory, the burden of proof lies with the Examiner to provide extrinsic evidence that *makes clear* that the missing descriptive matter (*i.e.*, enhancing the efficacy of a chemotherapeutic agent) is *necessarily present* in the methods of Falk *et al.* See M.P.E.P. § 2112 (IV), citing *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999). Moreover, inherency may not be established by *probabilities* or *possibilities*, and the mere fact that a certain characteristic *may* occur or be present in the prior art is *not sufficient* to establish the inherency of that characteristic. *Id.* Here, the Examiner has provided no extrinsic evidence to *make clear* that the administration step as performed in Falk *et al.* would *necessarily* enhance the efficacy of a chemotherapeutic agent for a cancer cell, as disclosed in the instant specification and recited in the instant claims. The Examiner, thus, has failed to establish by the requisite extrinsic evidence that the method of Falk *et al.* inherently discloses each feature of the instant claims.

Moreover, the evidence of record suggests the contrary. For instance, this evidence shows that lower molecular weight forms of hyaluronan, *i.e.*, less than 400,000 Da, have entirely different structural and functional features as compared to higher molecular weight forms of hyaluronan (*see, e.g.*, Item 4 of the Declaration of Dr. Tracy Brown). In particular, the preferred, lower molecular weight hyaluronan embodiments, *i.e.*, less than 400,000 Da, relied upon in Falk *et al.* are incapable of forming the complex tertiary structures required for effective small molecule incorporation for delivery of such drugs to a target site. *Id.* In view of this evidence, and further in view of the Examiner's failure to provide the requisite extrinsic evidence to the contrary, Falk *et al.* fail to make clear that the particular methods described therein

necessarily enhance the efficacy of a chemotherapeutic agent, as with the presently claimed compositions of hyaluronan having a molecular weight between 400,000 and 900,000 Da.

Applicant also notes that when the prior art is alleged to disclose a range which touches or overlaps the claimed range, but no specific examples falling within the claimed range are disclosed, the claimed subject matter must be disclosed in the reference with “sufficient specificity to constitute an anticipation under the statute.” See M.P.E.P. § 2131.03 (II). As one application of this rule, in *Atofina v. Great Lakes Chem. Corp.*, a reference temperature range of 100-500°C did not describe the claimed range of 330-450°C with “sufficient specificity” to be anticipatory. 441 F.3d 991, 999 (Fed. Cir. 2006). In *Atofina*, there was even a slight overlap between the prior art reference's preferred range and the claimed range, but even this overlap was not sufficient for anticipation. *Id.* Here, Falk *et al.* does not specifically disclose the use of a composition comprising a chemotherapeutic agent and hyaluronan, wherein the hyaluronan has a molecular weight in the range of 400,000 to 900,000 Da. Instead, as best can be determined from the Examples provided therein, Falk *et al.* merely rely upon certain preferred embodiments, each of which falls *outside* the presently claimed range (*see, e.g.*, column 17, lines 33-42; and column 18, lines 8-10). As such, more so than in *Atofina*, the hyaluronan molecular weight range of Falk *et al.* does not disclose with “sufficient specificity” the claimed range of 400,000 to 900,000 Da, especially since this claimed range not only possesses critical features unappreciated by Falk *et al.*, as exemplified above (*see* Item 4 of the Declaration of Dr. Tracy Brown), but does not overlap at all with the 150,000 to 225,000 Da preferred embodiments described therein. The disclosure in Falk *et al.*, thus, fails to constitute an anticipation under § 102(e).

Since Falk *et al.* fail to teach, either explicitly or inherently, each feature of the instant claims, and further fail to described the presently claimed range with “sufficient specificity,” Applicant submits that the instant claims satisfy the requirements of novelty over Falk *et al.*, and respectfully request withdrawal of this rejection under 35 U.S.C. § 102(e).

With regard to the obviousness rejection under § 103(a), Applicant submits that the Examiner has not established a *prima facie* case of obviousness. *See In re Mayne*, 104 F.3d 1339 (Fed. Cir. 1997) (The USPTO has the burden of showing a *prima facie* case of

obviousness). At a minimum, it must be demonstrated that the cited reference teaches or suggests all the claim features, and even assuming, *arguendo*, that the cited reference teaches each claim feature, the Examiner must provide an explicit, apparent reason to combine these features in the fashion claimed by the Applicant with a reasonable expectation of success. *See KSR v. Teleflex, Inc.*, No. 04-1350 at 4, 14 (U.S. Apr. 30, 2007) (“A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art”). Here, as discussed above, Falk *et al.* do not teach or suggest, either explicitly or inherently, that the efficacy of a chemotherapeutic agent may be enhanced by administering a composition containing hyaluronan and the agent, and further fail to provide a person of ordinary skill in the art at the time of filing with a motivation to practice the presently claimed subject matter with a reasonable expectation of success.

A person skilled in the art would not have been motivated to modify the compositions of Falk *et al.* for use with cancer therapy, in the particular fashion claimed by Applicant, with a reasonable expectation of success. To the contrary, as evidenced by the Declaration of Dr. Tracey Brown, the modifications suggested by the Examiner would have rendered the composition of Falk *et al.* inoperable or unsatisfactory for its intended purpose as described in that reference, which is “to facilitate the agent’s penetration ***through the tissue*** (including scar tissue), at the site to be treated through the cell membranes into the individual cells to be treated” (*see, e.g.*, column 10, lines 36-43) (emphasis added). Specifically, the evidence of record shows that compositions comprising hyaluronan at a molecular weight of more than 400,000 Da (*e.g.*, 700,000 Da), as presently claimed, do not facilitate tissue penetration in the manner relied upon by the method of Falk *et al.* (*see, e.g.*, Items 5 and 6 in the Declaration of Dr. T. Brown), rendering them unsatisfactory for the specific purpose described therein. This premise is supported by the only preferred embodiments in Falk *et al.*, which rely on lower molecular weight hyaluronan compositions shown to penetrate tissues, such as those in the range of 150,000 to 225,000 Da (*see, e.g.*, column 17, lines 33-42 of Falk *et al.*; and Item 6 of the Declaration of Dr. T. Brown). Applicant notes that if a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. M.P.E.P. § 2143.01, citing *In re*

Gordon, 733 F.2d 900 (Fed. Cir. 1984). If there is no motivation to make the proposed modification with a reasonable expectation of success, then there can be no *prima facie* case of obviousness. *KSR v. Teleflex* No. 04-1350 (U.S. Apr. 30, 2007).

Nonetheless, even assuming, *arguendo*, that the Examiner has fairly established a *prima facie* case of obviousness with regard to the claimed molecular weight range of hyaluronan, any evidence of unexpected results within the claimed range may render the claims non-obvious. See M.P.E.P. §§ 2131.03 (II) & 2144.05, citing *In re Woodruff*, 919 F.2d 1575 (Fed. Cir. 1990). Here, the evidence of record shows that a person of ordinary skill in the art at the time of filing would have expected higher molecular weight hyaluronan-based compositions to have an **undesirable** viscosity for therapeutic administration, especially for the type of **systemic** administration that would have been recognized as relevant to cancer therapy (*see, e.g.*, Item 8 in the Declaration of Dr. T. Brown). For instance, the evidence of record teaches that compositions of hyaluronan having increased molecular weight (*e.g.*, 400,000 to 750,000 Da or above) are highly viscous, such that their **systemic** administration would have been expected to lead to either hyper-viscosity syndrome, the formation of occlusions to blood vessels, and/or the formation of emboli or thrombosis. Falk *et al.* does not contradict this expectation, since, as noted herein, this reference relies on preferred, lower molecular weight hyaluronan compositions. Applicant, however, demonstrated empirically in Phase I and II clinical trials that such compositions not only fail to cause adverse side effects upon intravenous administration (*see* Item 8 of the Declaration of Dr. T. Brown), but provide significant therapeutic benefits in cancer therapy, and have been accepted by the Food and Drug Administration (FDA) for phase III trials (*see, e.g.*, Item 7 of the Declaration of Dr. T. Brown). These unexpected results contradict the expectations of a person of ordinary skill in the art at the time of filing, and, thereby, demonstrate the non-obviousness of the presently claimed subject matter.

Given the deficiencies in Falk *et al.* in failing to provide a motivation to practice the presently claimed subject matter with a reasonable expectation of success, in combination with the unexpected benefits described by Applicant in using higher molecular weight hyaluronan compositions in the type of therapeutic administration relevant to cancer therapy, Applicant submits that the instant claims satisfy the requirements of non-obviousness over Falk

et al. Accordingly, Applicant respectfully requests withdrawal of this rejection under 35 U.S.C. § 103(a).

Rejection Under 35 U.S.C. § 102

The Examiner rejected claims 27-28, 32-34, 38-40, 44-46, and 50 under 35 U.S.C. § 102(b) for alleged lack of novelty over della Valle *et al.* (U.S. Patent No. 5,422,053). The Examiner asserts that della Valle *et al.* disclose the use of compositions comprising chemotherapeutic agents in combination with HA having a molecular weight between 300,000 and 730,000 Da.

Applicant traverses this rejection and submits that the instant claims satisfy the requirements of novelty over della Valle *et al.* Similar to Falk *et al.*, Applicant submits that della Valle *et al.* fail to teach, either explicitly or inherently, each feature of the instant claims, and in particular fail to teach or suggest that the efficacy of a chemotherapeutic agent may be enhanced by administering a composition containing hyaluronan and the agent.

della Valle *et al.* do not disclose, inherently or explicitly, that the hyaluronic acid (HA) based compositions provided therein may be utilized to enhance the efficiency of a chemotherapeutic agent. Rather, as noted above, to rely on an inherency theory, the burden of proof lies with the Examiner to provide extrinsic evidence that *makes clear* that the missing descriptive matter (*i.e.*, enhancing the efficacy of a chemotherapeutic agent) is *necessarily present* in the methods of della Valle *et al.* See M.P.E.P. § 2112 (IV), citing *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999). Moreover, inherency may not be established by *probabilities* or *possibilities*, and the mere fact that a certain characteristic *may* occur or be present in the prior art is *not sufficient* to establish the inherency of that characteristic. *Id.* Here, the Examiner has provided no required extrinsic evidence that the administration step as performed in della Valle *et al.* would inherently enhance the efficacy of a chemotherapeutic agent for a cancer cell, as disclosed in the instant specification and recited in the instant claims.

The Examiner's failure to provide such extrinsic evidence is particularly problematic in view of the limited teachings in della Valle *et al.*, which do not in any way relate to cancer therapy. For instance, della Valle *et al.* teach that the higher molecular weight

hyaluronan compositions described therein are suitable only for certain limited therapeutic applications, such as topical, intra-ocular, and intra-articular administration (*see, e.g.*, column 3, lines 62-64; and column 4, lines 13-23). The presently claimed methods, however, relate to enhancing the efficacy of cancer therapy, which typically is not achieved through topical, intra-ocular, and intra-articular administration of chemotherapeutic agents, as described in della Valle *et al.*, but is instead more typically achieved through intravenous or systemic administration (*see, e.g.*, page 27, lines 19-24 of the instant specification). As such, a person skilled in the art would not expect the particular steps of administration described in della Valle *et al.* to ***necessarily*** enhance the efficacy of a chemotherapeutic agent to a cancer cell, as recited in the instant claims.

In view of the deficiencies in della Valle *et al.*, which does not explicitly or inherently describe the use of higher molecular weight hyaluronan compositions to enhance the efficacy of a chemotherapeutic agent, Applicant submits that the presently claimed method represents a new use of previously described compound. To this end, the Federal Circuit has consistently held that a new use of a previously known device or method is patentable. *See, e.g., In re King*, 801 F.2d 1324, 132 (Fed. Cir. 1986).

Applicant, thus, submits that the instant claims satisfy the requirements of novelty over della Valle *et al.*, and respectfully requests withdrawal of this rejection under 35 U.S.C. § 102(b).

Rejection Under 35 U.S.C. § 103

The Examiner rejected claims 27, 29-31, 35-38, 41-43, 47-79, and 51-52 under 35 U.S.C. § 103(a) for alleged obviousness over della Valle *et al.* The Examiner agrees that della Valle *et al.* do not disclose hyaluronan having a molecular weight of 750,000 Da or above in a composition with a chemotherapeutic agent, as presently claimed, but asserts that a person of ordinary skill in the art would have had a reasonable expectation of success in creating such a composition to provide a carrier vehicle having the desired viscosity, and, thus, to provide the desired therapeutic benefits of improved drug efficacy.

Applicant traverses this rejection and submits that the instant claims satisfy the requirements of non-obviousness. Applicants submits that the Examiner has failed to establish a

prima facie case of obviousness over the presently claimed subject matter. For one, as conceded by the Examiner, della Valle *et al.* fail to teach or suggest the therapeutic use of hyaluronan having a molecular weight of 750,000 Da or above, as recited in the instant claims. In addition, the Examiner has not established the requisite motivation to modify the teachings of della Valle *et al.* in arriving at the presently claimed subject matter with a reasonable expectation of success.

della Valle *et al.* does not teach or suggest each feature of the instant claims, and in particular does not teach or suggest the therapeutic administration of hyaluronan having a molecular weight of 750,000 Da or above to enhance efficacy of a chemotherapeutic agent to a cancer cell. To the contrary, the cited reference discloses, at best, the administration of hyaluronan having a molecular weight below 730,000 Da by intra-ocular, intra-articular, and intra-dermal routes, and does not in any way suggest that the presently claimed compositions may be utilized in the type of administration protocols relevant to cancer therapy, including, for example, systemic or intravenous administration. della Valle *et al.*, thus, fail to teach or suggest each feature of the instant claims.

Further, and contrary to the Examiner's assertion at page 8 of the Action, a person of ordinary skill in the art at the time of filing would not have reasonably expected that a composition of hyaluronan having a molecular weight of 750,000 Da would have provided a carrier having a viscosity suitable for enhancing the efficacy of a chemotherapeutic agent to a cancer cell. Indeed, the Examiner's conclusory assertion in this regard is unsupported by either any technical reasoning or the evidence of record. It is kindly noted that in failing to support this assertion, the Examiner has not provided the requisite technical reasoning to support the assertion of obviousness. *KSR* at 14, citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."). As such, the Examiner has not satisfied the burden of proof with regard to obviousness, and, thus, has not properly established a *prima facie* case of obviousness over della Valle *et al.*

Moreover, the evidence of record directly contradicts the Examiner's assertion that a person of ordinary skill in the art would have reasonably expected that a composition of

hyaluronan having a molecular weight of 750,000 Da would have resulted in a carrier having a desired viscosity. Rather, the Declaration of T. Brown evidences that such a person would have failed to expect higher molecular weight hyaluronan-based compositions to provide a desirable viscosity for therapeutic administration, especially for the type of **systemic** administration that would have been recognized as relevant to cancer therapy. For instance, the evidence of record teaches that compositions of hyaluronan having increased molecular weight (*e.g.*, 750,000 Da or above) are highly viscous, such that in the absence of Applicant's experimental evidence their systemic or intravenous administration would have been expected to lead to either hyper-viscosity syndrome, the formation of occlusions to blood vessels, and/or the formation of emboli or thrombosis (*see, e.g.*, Item 8 of the Declaration of T. Brown), none of which represent a desired therapeutic outcome. Consistent with this understanding, della Valle *et al.* also teach that the higher weight hyaluronan compositions described therein (*e.g.*, less than 730,000 Da) have high viscosity, making them suitable only for limited therapeutic purposes, such as topical, intra-ocular, and intra-articular administration (*see, e.g.*, column 3, lines 62-64; and column 4, lines 13-23). The evidence of record, therefore, not only contradicts the Examiner's assumed motivation and reasonable expectation of success in arriving at the presently claimed subject matter, but teaches away from the same, thereby supporting a conclusion of non-obviousness under § 103(a).

Given the deficiencies in della Valle *et al.*, Applicant submits that the instant claims, related to compositions comprising hyaluronan with a molecular weight of more than about 750,000 Da for use in enhancing efficacy of cancer therapy, satisfy the requirements of non-obviousness over della Valle *et al.*, and respectfully request withdrawal of this rejection under 35 U.S.C. § 103(a).

Applicant believes that all of the claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Application No. 09/889,203

Reply to Office Action dated February 20, 2008

Respectfully submitted,

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Enclosures

Declaration of Dr. Tracey Brown

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